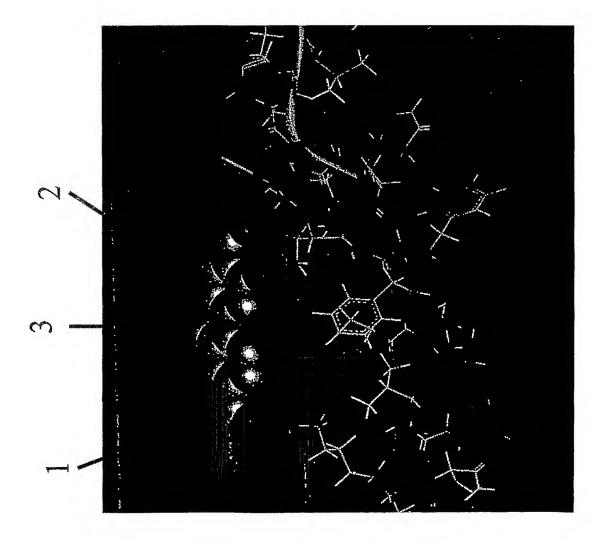
FIGURE 1

- 1 Helix stabilizationby selective electrostaticinteractions
- 2 Helix stabilization
 via interaction with the
 rigid hydrophobic scaffold
- 3 Combinatorially varied substituents



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"Morphomer" concept

FIGURE 2

• Molecular scaffolds are designed complementary to A β helical (soluble) structure

 Conformational restrictions are introduced to partially lock each set of conformations (morphology) of library components • Libraries formed on the basis of scaffolds explore both chemical (Rx) and conformational diversity space

-000

FIGURE 3

Molecular Adaptation of Morphomers to the Target Leads to Formation of Stronger Complexes

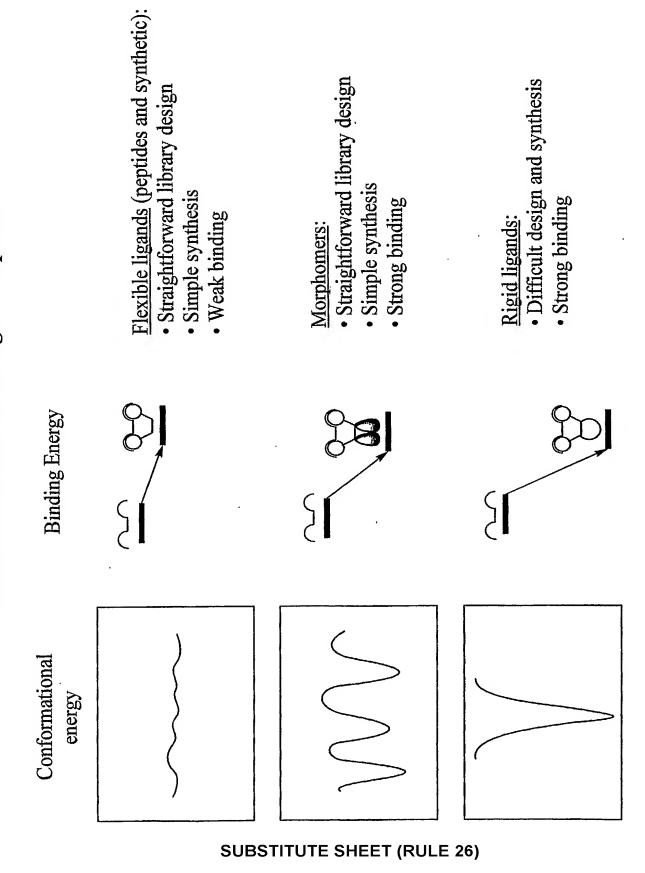


FIGURE 4

General Strategy of Small Molecules – 8-Sheet breakers for Therapy of Alzheimer's Disease by mass spectrometry solubilization assay + analysis of hits Fluorescent AB complementation 3. Screening **B-Galactosidase** In vivo HTS In vitro assay Scaffold synthesis generation 2. Library Morphomer concept focused design of components ibraries of small molecules – capable of crossing BBB Know-how Bioavailability: **B-sheet breakers** 1. Design: structural design Proprietary

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Screening of Small Molecules for AB Solubilization Activity

In vitro

• Fluorescent Assay:

Aβ fiber stained with Thioflavin T solubilization/depolymerization is monitored by fluorescence decrease

· Mass spectrometry assay:

Complexes of amyloid with small molecules are detected and characterized by MS

Hits are fully structurally characterized using regiochemical taggig techniques (provisional patent application filed)

Solubility/ folding supernatant **Active blue blue conding supernatant **Active blue conding supernatant **Active blue conding supernatant **Active blue conding supernatant **Active blue conding condin

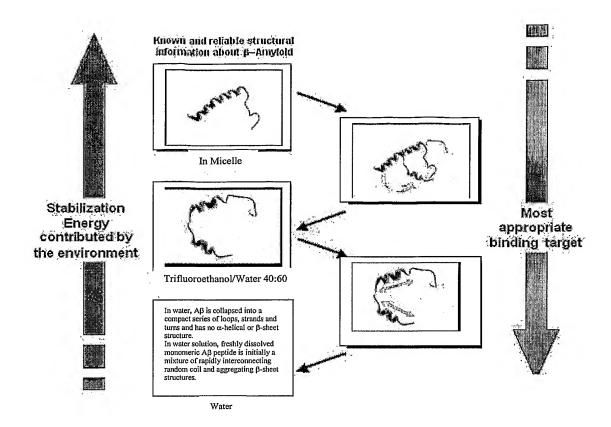
in vivo solubilization assay for Aβ (W.C. Wigley, et al. *Nature Biotechnol*. 2001, *19*, 131-136)

pellet

FIGURE 5

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Figure 6



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Figure 7

Molecular Design

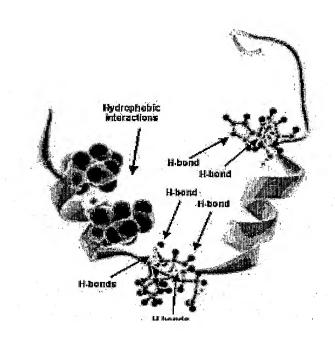


Figure 8

 \mathbf{A}

B

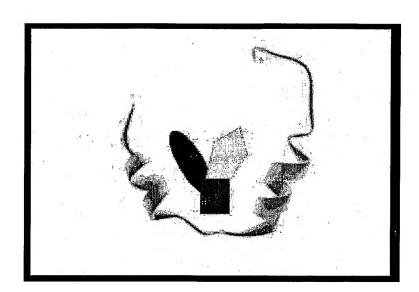


Figure 9